```
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FILE CONTENT:1840 - 7 Jun 2008 VOL 148 ISS 24

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This file contains CAS Registry Numbers for easy and accurate substance
identification.

=> d que
L1                STR
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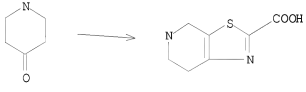


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Structure attributes must be viewed using STN Express query preparation.
L3            3 SEA FILE=CASREACT SSS FUL L1 (     5 REACTIONS)


=> d l3 1-3 ibib abs hit


L3   ANSWER 1 OF 3  CASREACT  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         141:395464  CASREACT
TITLE:                    Synthesis and Conformational Analysis of a Non-Amidine
                          Factor Xa Inhibitor That Incorporates
                          5-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine as
                          S4 Binding Element
AUTHOR(S):                Haginoya, Noriyasu; Kobayashi, Syozo; Komoriya,
                          Satoshi; Yoshino, Toshiharu; Suzuki, Makoto; Shimada,
                          Takashi; Watanabe, Kengo; Hirokawa, Yumiko; Furugori,
                          Taketoshi; Nagahara, Takayasu
CORPORATE SOURCE:         Medicinal Chemistry Research Laboratory, Daiichi
                          Pharmaceutical Co. Ltd, Edogawa-ku, Tokyo, 134-8630,
                          Japan
SOURCE:                   Journal of Medicinal Chemistry (2004), 47(21),
                          5167-5182
```
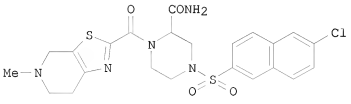
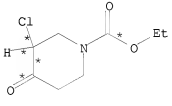

CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

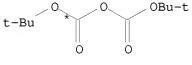
AB Our exploratory study was based on the concept that a non-amidine factor Xa (fXa) inhibitor is suitable for an orally available anticoagulant. We synthesized and evaluated a series of N-(6-chloronaphthalen-2-yl)sulfonylpiperazine derivs. incorporating various fused-bicyclic rings containing an aliphatic amine expected to be S4 binding element. Among this series, 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine type I displayed orally potent anti-fXa activity and evident prolongation of prothrombin time (PT) with the moderate bioavailability in rats. The X-ray crystal anal. afforded an obvious binding mode that 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine and 6-chloronaphthalene resp. bound to S4 and S1 subsites. In this X-ray study, we discovered a novel intramol. S-O close contact. Ab initio energy calcns. of model compds. deduced that conformers with the most close S-O proximity were most stable. The Mulliken population anal. proposed that this energy profile was caused by both of electrostatic S-O affinity and N-O repulsion. The results of these calcns. and X-ray anal. suggested a possibility that the restricted conformation effected the affinity to S4 subsite of fXa.
REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

RX(150) OF 352 COMPOSED OF RX(23), RX(24), RX(25)
RX(150) BY + BZ + B + BR ===> CD



BY

BZ



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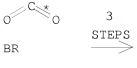
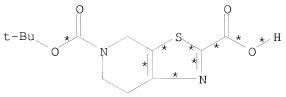


BR



CD
YIELD 82%

RX(23) RCT BY 89424-04-4, BZ 115-08-2
PRO CA 165948-22-1
SOL 71-36-3 BuOH
CON 2.5 hours, 100 deg C
NTE molecular sieves used

RX(24) RCT CA 165948-22-1

STAGE(1)
RGT N 1310-73-2 NaOH
SOL 7732-18-5 Water
CON SUBSTAGE(1) 2 hours, 110 deg C
SUBSTAGE(2) 110 deg C -> room temperature

STAGE(2)
RCT B 24424-99-5
SOL 67-56-1 MeOH
CON 2 hours, room temperature

STAGE(3)
RGT AH 7647-01-0 HCl
SOL 7732-18-5 Water
CON room temperature, pH 2 - 3

PRO CC 165948-24-3

RX(25) RCT CC 165948-24-3

STAGE(1)
RGT BT 109-72-8 BuLi
SOL 60-29-7 Et2O, 110-54-3 Hexane
CON 15 minutes, -78 deg C

STAGE(2)
RCT BR 124-38-9
CON 5 minutes, -78 deg C

PRO CD 365996-70-9

L3 ANSWER 2 OF 3 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 141:225377 CASREACT

TITLE: Facile methods for preparation of thiazolopyridine and tetrahydrothiazolopyridine derivatives

AUTHOR(S): Haginoya, Noriyasu; Komoriya, Satoshi; Osanai, Ken; Yoshino, Toshiharu; Nagata, Tsutomu; Nagamochi, Masatoshi; Muto, Ryo; Yamaguchi, Mitsuhiro; Nagahara, Takayasu; Kanno, Hideyuki

CORPORATE SOURCE: Medicinal Chemistry Research Laboratory, Daiichi Pharmaceutical Co., Ltd, Tokyo, 134-8630, Japan

SOURCE: Heterocycles (2004), 63(7), 1555-1561
CODEN: HTCYAM; ISSN: 0385-5414

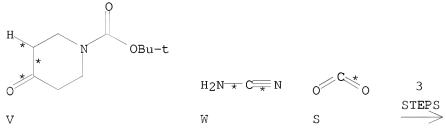
PUBLISHER: Japan Institute of Heterocyclic Chemistry

DOCUMENT TYPE: Journal

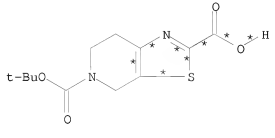
LANGUAGE: English

AB Improved routes to prepare tetrahydrothiazolo[5,4-c]pyridine-2-carboxylic acid lithium salts were developed. Route A consisted of the improved preparation of thiazolopyridine intermediates, and Route B is applicable for a large scale synthesis of tetrahydrothiazolo[5,4-c]pyridine-2-carboxylic acid derivs. The methods may serve as facile means for preparing thiazolopyridine and tetrahydrothiazolopyridine derivs.

RX(31) OF 33 COMPOSED OF RX(9), RX(10), RX(13)
RX(31) V + W + S ===> AO



V W S



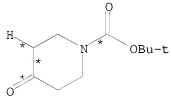
● Li

AO
YIELD 66%

RX(9) RCT V 79099-07-3

STAGE(1)
RGT Y 123-75-1 Pyrrolidine

```
               CAT  104-15-4 TsOH
               SOL  110-82-7 Cyclohexane
               CON  2 hours, reflux

             STAGE(2)
               RCT  W 420-04-2
               RGT  D 10544-50-0 S8
               SOL  67-56-1 MeOH
               CON  SUBSTAGE(1) 0 deg C
                    SUBSTAGE(2) 5 hours, 0 deg C

           PRO  X 365996-05-0
           NTE  scalable, >100 g

RX(10)     RCT  X 365996-05-0
           RGT  AD 540-80-7 t-BuONO, AE 7789-45-9 CuBr2
           PRO  AC 365996-06-1
           SOL  68-12-2 DMF
           CON  SUBSTAGE(1) 50 deg C
                SUBSTAGE(2) 2 hours, 50 - 60 deg C
           NTE  scalable, >100 g

RX(13)     RCT  AC 365996-06-1

             STAGE(1)
               RGT  C 109-72-8 BuLi
               SOL  60-29-7 Et2O, 110-54-3 Hexane
               CON  SUBSTAGE(1) -78 deg C
                    SUBSTAGE(2) 20 minutes, -78 deg C

             STAGE(2)
               RCT  S 124-38-9
               CON  SUBSTAGE(1) 5 minutes, -78 deg C
                    SUBSTAGE(2) -78 deg C -> room temperature

           PRO  AO 365996-70-9


RX(33) OF 33 COMPOSED OF RX(9), RX(10), RX(11), RX(12)
RX(33)     V  +  W  +  AF  +  S  ===>  U
```



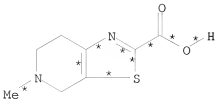
V

W

AF

S

4 STEPS



● Li

U
YIELD 99%

RX(9) RCT V 79099-07-3

STAGE(1)
RGT Y 123-75-1 Pyrrolidine
CAT 104-15-4 TsOH
SOL 110-82-7 Cyclohexane
CON 2 hours, reflux

STAGE(2)
RCT W 420-04-2
RGT D 10544-50-0 S8
SOL 67-56-1 MeOH
CON SUBSTAGE(1) 0 deg C
SUBSTAGE(2) 5 hours, 0 deg C

PRO X 365996-05-0
NTE scalable, >100 g

RX(10) RCT X 365996-05-0
RGT AD 540-80-7 t-BuONO, AE 7789-45-9 CuBr2
PRO AC 365996-06-1
SOL 68-12-2 DMF
CON SUBSTAGE(1) 50 deg C
SUBSTAGE(2) 2 hours, 50 - 60 deg C
NTE scalable, >100 g

RX(11) RCT AC 365996-06-1

STAGE(1)
RGT AH 76-05-1 F3CCO2H
SOL 75-09-2 CH2Cl2
CON 10 minutes, room temperature

STAGE(2)
RCT AF 50-00-0
RGT AI 56553-60-7 Na.(AcO)3BH, AJ 121-44-8 Et3N, AK 64-19-7 AcOH
SOL 7732-18-5 Water, 75-09-2 CH2Cl2
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(3)

RGT AL 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature

PRO AG 143150-92-9
NTE scalable, 50 g

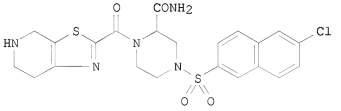
RX(12) RCT AG 143150-92-9

STAGE(1)
RGT C 109-72-8 BuLi
SOL 60-29-7 Et2O, 110-54-3 Hexane
CON SUBSTAGE(1) -78 deg C
SUBSTAGE(2) -78 deg C -> 0 deg C
SUBSTAGE(3) 20 minutes, 0 deg C
SUBSTAGE(4) 0 deg C -> -78 deg C

STAGE(2)
RCT S 124-38-9
CON SUBSTAGE(1) 5 minutes, -78 deg C
SUBSTAGE(2) -78 deg C -> room temperature

PRO U 259809-25-1
NTE scalable, 50 g

L3 ANSWER 3 OF 3 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 141:123587 CASREACT
TITLE: Orally active factor Xa inhibitors: 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine derivatives
AUTHOR(S): Haginoya, Noriyasu; Kobayashi, Syozo; Komoriya, Satoshi; Hirokawa, Yumiko; Furugori, Taketoshi; Nagahara, Takayasu
CORPORATE SOURCE: Medicinal Chemistry Research Laboratory, Daiichi Pharmaceutical Co. Ltd., Edogawa-ku, Tokyo, 134-8630, Japan
SOURCE: Bioorganic & Medicinal Chemistry Letters (2004), 14(11), 2935-2939
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



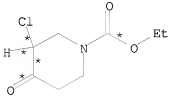
I

AB In an investigation of factor Xa inhibitors, a series of 1-(6-chloronaphthalen-2-yl)sulfonyl-4-(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carbonyl)piperazines were synthesized. In vitro inhibitory activities of the compds. against factor Xa and coagulation are

summarized. Among these, 4-[(6-chloro-2-naphthalenyl)sulfonyl]-1-[(4,5,6,7-tetrahydro-5-methylthiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-piperazinecarboxamide (I) and 4-[(6-chloro-2-naphthalenyl)sulfonyl]-N-methyl-1-[(4,5,6,7-tetrahydro-5-methyloxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-piperazinecarboxamide, possessing a carbamoyl or N-methylcarbamoyl moiety, showed potent inhibitory activities when administered orally to rats.

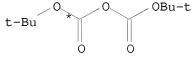
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

RX(61) OF 188 COMPOSED OF RX(3), RX(4), RX(1)
RX(61) L + M + P + B ===> C



L

M



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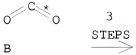

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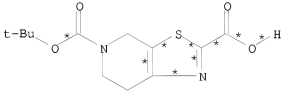


● Li

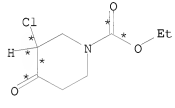
C
YIELD 85%

RX(3) RCT L 89424-04-4, M 115-08-2
PRO N 165948-22-1
SOL 64-17-5 EtOH
NTE 4Å MS used

RX(4) RCT N 165948-22-1

STAGE(1)
RGT Q 121-44-8 Et3N
SOL 7732-18-5 Water

```
            STAGE(2)
               RCT   P 24424-99-5

            PRO   A 165948-24-3

RX(1)       RCT   A 165948-24-3

            STAGE(1)
               RGT   D 109-72-8 BuLi
               SOL   60-29-7 Et2O

            STAGE(2)
               RCT   B 124-38-9

            PRO   C 365996-70-9


RX(62) OF 188 COMPOSED OF RX(3), RX(5), RX(25)
RX(62)      L  +  M  +  B  ===>  F
```

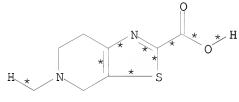


L

M

B

3
STEPS



● Li

```
F
YIELD 100%


RX(3)       RCT   L 89424-04-4, M 115-08-2
            PRO   N 165948-22-1
            SOL   64-17-5 EtOH
            NTE   4Å MS used

RX(5)       RCT   N 165948-22-1
            RGT   T 16853-85-3 LiAlH4
            PRO   S 259809-24-0
            SOL   60-29-7 Et2O
```

```
RX(25)    RCT  S 259809-24-0

            STAGE(1)
               RGT  D 109-72-8 BuLi
               SOL  60-29-7 Et2O

            STAGE(2)
               RCT  B 124-38-9

          PRO  F 259809-25-1
```

=>